HEB and E2A function as SMAD/FOXH1 cofactors.

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Public Summary:
Nodal signaling, using the Smad proteins, is critical for the formation of the fetus and for adult health. In this work, we have identified now proteins that interact with the Smads and find that these proteins are essential for proper Nodal signaling in stem cells and in development. These newly identified Smad components, the E proteins, have been extensively studied for their role in blood formation. They serve as important new candidates for stem cell biology and human diseases such as cancer and fibrosis that are known to have a Nodal component.

Scientific Abstract:
Nodal signaling, mediated through SMAD transcription factors, is necessary for pluripotency maintenance and endoderm commitment. We identified a new motif, termed SMAD complex-associated (SCA), that is bound by SMAD2/3/4 and FOXH1 in human embryonic stem cells (hESCs) and derived endoderm. We demonstrate that two basic helix-loop-helix (bHLH) proteins-HEB and E2A-bind the SCA motif at regions overlapping SMAD2/3 and FOXH1. Furthermore, we show that HEB and E2A associate with SMAD2/3 and FOXH1, suggesting they form a complex at critical target regions. This association is biologically important, as E2A is critical for mesendoderm specification, gastrulation, and Nodal signal transduction in Xenopus tropicalis embryos. Taken together, E proteins are novel Nodal signaling cofactors that associate with SMAD2/3 and FOXH1 and are necessary for mesendoderm differentiation.